

**Assessing the Coronary Artery Calcium Score:
a Systematic Review of Cost-Effectiveness and
an Exploratory Association with
Masked Hypertension**

By

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Abstract

Coronary heart disease (CHD) remains the leading cause of death in the United States despite the widespread use of statin therapy in primary prevention. Currently, global risk assessments such as the Framingham risk score estimate the 10-year risk for a CHD event for the purpose of guiding who should receive preventive treatment. As clinicians seek to improve the accuracy and validity of such risk estimation, additional screening methods have been introduced. The coronary artery calcium (CAC) scan is one such method shown to improve net risk classification, although its cost-effectiveness of the scan and its association with other risk factors such as hypertension remain inconclusive.

The CAC score (Agatston units) is a strong independent predictor of CHD events and its use in CHD prediction models improves net risk classification more than any other nontraditional risk factor. As a screening tool, its utilization is to direct which patients receive statin therapy from the resulting risk prediction. However, when making a clinical decision to use a screening test, the benefits of the test and resulting treatment must be weighed against the costs and harms. Cost-effective analysis are one way to estimate such utility of a screening tool such as the CAC scan.

Another independent risk factor for CHD events is masked hypertension; the phenomenon of having normal office blood pressure readings while having elevated ambulatory blood pressure readings. Masked hypertension reaches levels of CHD risk similar to sustained hypertension, and yet its association with another nontraditional risk factor, CAC, has never been explored.

The aim of this master's paper is two-fold; first, to assess the cost-effectiveness of the CAC scan guiding statin therapy versus a broad treatment strategy; second, to explore if patients with MH are more likely to have CAC present than those with sustained normotension.

A Systematic Review of the Cost-Effectiveness of Coronary Artery Calcium Screening Guiding Statin Therapy for Primary Cardiovascular Heart Disease Prevention

Abstract

Introduction: Coronary heart disease (CHD) remains the leading cause of death in the United States despite the widespread use of statin therapy in primary prevention. Currently, global risk assessments such as the Framingham risk score estimate the 10-year risk for a CHD event for the purpose of guiding preventive treatment. As clinicians seek to improve the accuracy and validity of such risk estimation, additional screening methods have been introduced. The coronary artery calcium (CAC) scan is one such method shown to improve net risk classification, although the additional harms and cost of the scan is an important factor that should be evaluated. Cost-effective analysis (CEA) studies have been conducted in order to estimate such costs, benefits, and harms of using a CAC score to guide statin therapy compared to a treatment strategy based on risk estimated from validated risk calculators or a treat-all method.

Methods: PubMed and article references were searched for relevant CEA studies comparing CAC guiding therapy to broad statin treatment. Included studies must have used an analytical method (e.g. cost-analysis, cost-effectiveness, cost-benefit, cost utility) conducted in the last 10 years, with a clear primary outcome measure (e.g. QALY, life-years gained), provided information on the data source, and have been conducted in one or more Established Market Economies as defined by the World Bank. The included articles were systematically evaluated for comparative data and quality assessment using recommendations from the Cost-Effectiveness in Health and Medicine Task Force

Results: The review included three studies for full data extraction with one receiving a quality rating of “poor” and two of “good”. The poor study was presented as an editorial but included

an original analysis that provided a valuable perspective, finding that broad statin therapy may be more cost-effective than using CAC to guide therapy. The two “good” studies used Markov models to find different results. One found that CAC screening was the optimal decision for men, while the Framingham risk score was optimal for women. The other study found that broad statin therapy was optimal for both men and women. Both studies had different assumptions that influenced the results greatly.

Conclusions: There have been few studies assessing the cost-effectiveness of CAC scans directing statin therapy in patients with intermediate 10-year CHD risk estimates with inconclusive results. The conclusions of such studies vary greatly depending on the input variables, but it remains clear that CAC scans for widespread screening for primary prevention is not cost-effective.

Introduction

Cardiovascular disease (CVD) continues to burden the United States population with high morbidity, mortality, and health care costs. Almost 2 out of 3 men and over half of women aged 45 years and free of known disease will develop CVD over their lifetime.¹ By 2030, it is estimated that 44% of the US population will have some form of CVD.² Myocardial infarctions (MI) and other forms of coronary heart disease (CHD) cause over 32% of US deaths while costing \$315.4 billion in direct and indirect costs.¹ Many of these deaths occur in asymptomatic patients with no known CVD or overt risk-factors. Currently, primary prevention strategies include lifestyle changes and the possibility of pharmacotherapy using a statin.^{3,4} Deciding which asymptomatic patients would benefit from the use of a statin remains a challenging task, and the decision must balance the benefits, harms, and costs of the screening and treatment.

Coronary artery calcium and risk assessment

CHD risk prediction models provide 10-year estimates of future CHD events for asymptomatic individuals to assist treatment decisions. The Framingham risk calculator is widely adopted to stratify patients into low (<10% 10-year risk), intermediate (10% to 20% 10-year risk), and high (>20% 10-year risk) categories, although this method is imperfect and new risk assessment tools are becoming increasingly common.⁵ Additional risk factors and screening modalities have been identified to add further prognostic value including brachial artery reactivity testing, aortic and carotid magnetic resonance imaging, tonometric methods of measuring vascular compliance, and C-reactive protein, although the outcome data is lacking and the utility of these methods remains unclear.⁶

Coronary artery calcium (CAC) scans measure the amount of calcified atherosclerosis in coronary arteries through noninvasive computed tomography (CT) imaging. The CAC score (Agatston units) provides a quantitative measure that is a strong independent predictor of CHD

events.^{7, 8} Utilization of the CAC score in CHD prediction models improves net risk classification more than any other nontraditional risk factor.⁶⁻⁸ Polonsky et al found that when CAC was added to the Framingham risk model, 23% of the intermediate risk participants who developed CHD were correctly reclassified into the high risk group, while 13% who did not develop CHD were correctly reclassified into the low risk group.⁸

Using CAC score to guide statin treatment

Lifestyle modification remains a critical component of primary risk reduction including heart healthy diet, regular exercise habits, avoidance of tobacco products and maintenance of an optimal healthy weight.³ However, in patients with a moderate to high CHD risk, statins are an important addition to lifestyle modifications as they have been shown to reduce the risk of developing CVD in adults without a prior cardiac event.^{4, 9} Current guidelines from the American Heart Association recommend consideration of statin therapy for all patients with 7.5% or higher 10-year CHD event risk.⁴ These same guidelines also suggest that CAC scans may benefit intermediate risk patients by reclassifying them into a lower or higher risk group, thereby changing statin indication.⁴ A single study has shown that targeting statin therapy based on the CAC score improves CHD outcomes but potential costs and harms were not included in the analysis.¹⁰

When making a clinical decision to use a screening test, the harms of the test and the resulting intervention must be considered. Using statins for primary prevention in healthy individuals exposes them to costs and potential adverse drug effects^{11, 12} while CAC scans expose patients to small doses of ionizing radiation and add up-front costs.¹³ The cost of cardiovascular imaging is significant with Medicare fee-for service payments to cardiologists totaling \$5.8 billion, representing almost 9% of payments for all physician services.¹⁴ In a time

where health care costs are central to policy making,¹⁵ the cost-effectiveness of screening tests should be considered when their clinical utility is unclear. This paper aims to systematically review primary studies to evaluate the cost-effectiveness of CAC scan directing statin therapy versus broad statin therapy for primary prevention of CHD in asymptomatic patients.

Methods

Search Strategy

We conducted a systematic review of the literature of cost-effective analyses (CEAs) of CAC guiding statin therapy. Published studies were identified by PubMed search from April 2004 to April 2014 to identify relevant articles. We used the following search terms: (*“Cost effectiveness” OR “cost analysis” OR “health economics”*) AND (*“coronary artery calcium” OR “coronary calcium” OR “CAC” OR “calcium score”*) AND (*“statin” OR “HMG-CoA reductase inhibitors”*); the search was last conducted on April 23rd, 2014. We supplemented our findings with hand searches from the reference list of articles and reviews pending satisfaction of inclusion criteria.

Article Selection

Articles were selected based on standardized criteria for economic review methods.¹⁶ To be included studies must have used an analytical method (e.g. cost-analysis, cost-effectiveness, cost-benefit, cost utility), with a clear primary outcome measure (e.g. QALY, life-years gained), provided information on the data source, and have been conducted in one or more Established Market Economies as defined by the World Bank. The article must have reported the results of a primary study rather than a review or guideline and have been published in a peer-reviewed journal in the last 10 years. Additionally, the analytical method used must have compared the

utilization of CAC scores to guide selected statin therapy versus a broad treatment strategy. The search was limited to the English language only.

Data Extraction

Once an article was selected for full review, one author (BML) abstracted standardized information including study aim, study perspective, base case population description, analytical method, main results, sensitivity analysis, and harms evaluation. The same author also assessed quality of the study) using recommendations from the Panel on Cost-Effectiveness in Health and Medicine.¹⁷

Results

The initial PubMed search produced 25 titles. Six additional titles were selected from identified reviews. One author (BML) screened titles for relevance and those published before April 2004 were excluded. Ten abstracts were examined, and 7 were excluded because they did not evaluate CAC, statin, or were not a CEA study measuring consequences in natural units such as life years gained. Three articles underwent full text review and met the inclusion and exclusion criteria described above (Figure 1).¹⁸⁻²⁰

Study design

The three studies included in the review (Table 1) were cost-effective analysis measuring consequences in natural units. One analysis was presented as an editorial but was still a primary CEA that met the inclusion criteria described above.¹⁸ Two of the studies, also applied cost utility analysis that assessed consequences in terms of preference-based measures of health including quality adjusted life years.^{19, 20} These two studies used Markov models to assess the cost-effectiveness over a lifetime.

Study quality

Using recommendations from the Panel on Cost-Effectiveness in Health and Medicine¹⁷ two of the studies received a rating of “good”^{19, 20} while one received a rating of “poor” (Table 1 and Table 2).¹⁸ It is important to note that the “poor” study was an editorial intended to raise further exploratory analysis.

The Cost-Effectiveness of CAC Directing Statin Therapy

Each of the articles compared various screening and treatment strategies with different assumptions and costs for the CEAs. The results of each of the studies varied greatly when the estimates of costs and efficacy were changed to reflect uncertainty. We described the assumptions vital to each article before presenting the results and discussing the quality, strengths, and limitations of the findings.

The first article by Diamond & Kaul was an editorial article that included an assessment of the cost-effectiveness of three different screening and treatment strategies for 50 million middle-aged asymptomatic adults.¹⁸ Those three strategies included recommendations by the Screening for Heart Attack Prevention and Education (SHAPE), the 2002 National Cholesterol Education Program (NCEP) guidelines, and a treat all strategy with statins. These three strategies share a few assumptions including the treatment cost of a statin fixed at \$2/day and a one-time test of a Framingham-risk factor assessment at \$100 or an electron-beam computed tomography calcium scan at \$400. They assumed a non-screening or treatment CHD event rate of 1% in the 50 million person sample with 100,000 fatal and 400,000 non-fatal events. Each CHD event cost approximately \$100,000 in direct and indirect costs. Each fatal event is equivalent to a loss of 13 life-years and a non-fatal event of 4 life-years with each event representing a weighted loss of 6

life-year equivalents (LYEs). Patients were fully adherent to statin treatment and treatment reduced events by 30% independent of baseline characteristics.

The NCEP strategy proposed using one-time Framingham risk assessment to target statin therapy only to patients with a 10-year CHD risk > 20%. They assumed that 30% of the population will have the “high-risk” needed for statin treatment with 50% of the events will occur in this population. The SHAPE strategy proposed screening all 50 million with CAC and only treating those with a CAC score greater than 100 with a statin. They assumed that 25% of the population will have CAC score greater than 100 and 80% of the CHD events will occur in this population.

The study concluded that the treat all strategy was the most cost-effective. It would have the greatest net cost of \$21 billion, but it would also prevent the most events at 150,000. The marginal cost-effectiveness compared to the SHAPE strategy was \$22,000/LYE and \$28,000/LYE compared to the NCEP strategy, fulfilling the putative \$50,000/LYE threshold for cost-effectiveness.²¹ The next most cost-effective method was the CAC screening SHAPE strategy that reclassified patients into appropriate risk categories. Treating only the high-risk group after CAC screening will prevent 120,000 events at a net cost \$17 billion. The marginal cost-effectiveness of the SHAPE strategy versus the NCEP strategy was \$32,000/LYE. Lastly, the NCEP used the traditional Framingham risk tool to direct statin therapy would prevent 75,000 events at a net cost of \$8.3 billion.

This article was written as an editorial with the authors stating that the CEA was done with a “back of the envelope” style analysis. Both the strength and weaknesses of the article lie in the simplicity of the calculations. Previous articles have sought to compare the Framingham risk NCEP strategy to the CAC screening SHAPE strategy, however, such studies did not include a

“treat all” strategy for comparison.²² By including all three strategies for comparison, the authors were able to inform the readers of the potential cost-effectiveness of broad statin therapy utilization.

However, the study’s simple analysis failed to include vital aspects important to the validity of the CEA, which is why it was given a quality rating of “poor”. First, it did not include the potential harms of both screening and treatment besides upfront costs. A Framingham risk assessment could lead to multiple downstream follow-up clinical costs and additional pharmacotherapy if the risk was great enough. Low-dose radiation exposure of a CAC scan has a small but attributable cancer risk.¹³ Statins contain potential side effects such as myopathy, hepatitis, and quality of life disutility that cause a health and financial cost.^{11, 12} These were not included in the analysis or addressed in the discussion of the article.

As described above, CEAs rely on assumptions of benefits, costs and harms. These estimates should be evaluated in a sensitivity analysis to determine if small changes in these estimations lead to different outcomes. This article did not include a formal sensitivity analysis to determine which variable may have the largest influence on the outcome. It did discuss large swings in variables such as doubling treatment cost and halving screening costs, but these choices seemed clinically insignificant. A sensitivity analysis showing a decrease in treatment prices would have benefited the reader as the study used a fixed statin price of \$2/day and generics are available for \$4/month. Further sensitivity analysis including a variation in adherence rates also would have been helpful as the study assumes an impossible 100% adherence rate to statins.

The study by van Kempen et al. analyzed the cost-effectiveness and cost-utility of four different screening and treatment strategies of asymptomatic elderly men and women at intermediate-risk (10% to 20% 10-year CHD risk) as defined by the Framingham risk assessment

tool.¹⁹ The study used a Markov decision tree model to classify individuals into one of nine health states annually over a lifetime, including healthy, CHD event, major bleeding, stroke and major bleeding, CHD event and major bleeding, CHD event and stroke and major bleeding, CHD or stroke death, or non-CHD or non-stroke death. An important assumption for all four strategies included a treatment adherence rate of 70% of published clinical trial adherence rates which were applied to statins, antihypertensives and aspirin (ASA) therapy. The four strategies compared were identified as current practice, current guidelines, CAC screening for risk stratification, and treat-all with statin.

The current practice strategy served as the reference for CHD and non-CHD event rates and baseline statin, antihypertensives, and ASA therapy utilization for intermediate risk patients receiving no further screening or additional treatment. This data was extracted from the large-scale Rotterdam study.²³ The current guidelines strategy indicated statin therapy when low-density lipoprotein (LDL) exceeded 130 mg/dl and antihypertensive medication when systolic blood pressure (SBP) exceeded 140 mm Hg. The CAC screening strategy used a patient's CAC score to potentially reclassify them into a higher (> 20% 10-year CHD risk) or lower (< 10% 10-year CHD risk) Framingham. Those in the low-risk category would be treated with pharmacotherapy if SBP was above 140 mm HG and/or LDL levels were above 160 mg/dl. Those remaining in the intermediate-risk category would be treated as the current guidelines indicated above. All individuals reclassified into the high-risk category received lifestyle advice, statin therapy and antihypertensive medication. Men in this category would also receive a low-dose ASA (80 to 100 mg daily). The broad statin strategy would place all patients on a moderate dose statin and would otherwise be treated as current practice dictates.

The results of this lifelong Markov model was analyzed separately for men and women with differing conclusions. For men, CAC screening strategy was more effective and costly than all other three strategies. The incremental cost-effectiveness ratio (ICER) of CAC calcium screening was \$48,800/QALY gained reaching the theoretical “willingness-to-pay” threshold of \$50,000/QALY.²¹ The study did extensive sensitivity analysis that greatly varied the results. Using generic statin prices would drop the ICER of CAC screening in men to \$24,675/QALY gained. A shift in optimal decision would switch from CAC scanning to current guidelines if additional dyssynergy (compounded harms) of drugs occurred, if treatment adherence dropped below 58%, if the protective effect of ASA decreased, or if the cancer-radiation increased by 10-fold. Importantly, the optimal decision would also switch to current guidelines if the cost of CAC screening increased above \$200 (\$105 per scan used). Note that the other two studies in this review used \$400 and \$225 for the cost of a CAC scan.^{18, 20}

The model found that CAC screening in women is not cost-effective. The CAC screening was more effective and more costly than current practice or statin therapy, but was less effective and less costly than current guidelines. CAC screening was extended dominated by current guidelines because the latter leads to higher expected quality-adjusted life expectancy against a lower ICER. The ICER for current guidelines in women was \$51,400/QALY gained. The sensitivity analysis was less variable for women, with the optimal decision switching from current guidelines to broad statin therapy only if the combination of drugs carried an increased risk.

This study received a quality rating of “good” as it fulfilled the standards of most of the CEA checklist (Table 2). The sources of cost estimates, efficacy of pharmacotherapy, and event rates were clearly defined. The Markov model was fully explained and validated. Although it

covered a lifetime horizon for elderly patients, the model did have to assume CHD risk beyond 10 years which was adequately addressed in the discussion. The health risks and costs of the statins, ASA, and CAC screening were accounted for and included in the model. The study did a thorough sensitivity analysis with vital results noted above for both men and women.

The final study by Pletcher et al. found different results about the cost-effectiveness of CAC guiding statin therapy. The base-case scenario of this CEA was an asymptomatic 55-year-old women with an intermediate 10-year CHD risk of 7.5%. Five different scenarios were assessed with a Markov decision model. Two of the strategies included a treat-all with statin or treat-none with statin. Three others included a CAC scan where statin treatment was initiated with CAC score greater than 0, 100, or 300. With each of the five strategies, two treatment assumptions were analyzed. One included a favorable stain profile with generic pricing (\$4/month) and no reduction in quality of life from taking a daily pill. This was compared to a less favorable statin profile with a higher cost of \$1.00/pill and a quality of life penalty for taking a daily pill.

The Markov model showed that under favorable statin assumptions, the treat-all strategy would prevent 32 myocardial infarctions and add up to 1108 years to total life expectancy for 10,000 55-year old women at intermediate CHD risk. The next lowest-cost strategy is to treat those with a CAC score above 0, which would prevent 45% benefit of the treat all strategy. This gives the treat-all strategy an ICER of \$100/QALY gained. Under the less favorable statin assumptions, treat with CAC score above 0 proved most cost-effective with an ICER of \$18,000/QALY while the treat all strategy produced more QALYs at a higher cost and an ICER of \$78,000/QALY gained. The results for men at a 7.5% 10-year CHD risk were nearly identical although these results were not explained to detail in the article.

This study also received a quality rating of “good” as it addressed many of the same CEA areas as the van Kempen et al. article (Table 2).¹⁹ The sources of cost estimates, efficacy of pharmacotherapy, and event rates were clearly defined. The study included many health risks and costs of the statins and CAC screening. The study also did a thorough sensitivity analysis as described above.

One limitation was the article’s lack of detailed results for men. Although the base case was a woman, the CHD risk is even higher for men and therefore the cost-effectiveness of primary prevention strategies may be even more relevant to this subpopulation.¹

Discussion

The three CEAs included in this systematic review used different estimates and assumptions to compare various screening and treatment strategies concerning CAC and statin therapy. The “poor” quality study found that the treat-all strategy was more cost-effective than the CAC screening SHAPE guidelines or the Framingham screening NCEP guidelines.¹⁸ Two other articles received a quality rating of “good” with one concluding that CAC screening was the optimal strategy for men, while traditional current screening and treatment guidelines were optimal for women.¹⁹ The other found that a treat-all strategy would be the most cost-effective decision for men and women.²⁰

Limitations of results

It is difficult to directly compare the results of these studies to each other because of key differences in the estimates and assumptions. As discussed above, the editorial CEA used a limited analysis that lacked the inclusion of harms, downstream costs, and a complete sensitivity analysis. Although the other two studies used Markov models for the CEA, some vital

differences in their analysis make a direct comparison difficult. First, the base-case for each of the studies was quite different. They both used an asymptomatic adult with no prior CHD and an intermediate 10-year CHD risk. However, van Kempen et al. used an asymptomatic elderly person as the base-case with an average age older than 69 years, while Pletcher et al. used a 55 year old woman. Secondly, the source data used to estimate the CAC score distribution and risk classification was different between studies. Van Kempen et al. used the Rotterdam study²³ while Pletcher et al. used the MESA study¹⁰. Fourth, the pharmacotherapy directed at intermediate and high-risk CHD patients were different. Van Kempen et al. assumed statin, antihypertensive and ASA therapy while Pletcher et al. focused only on statin therapy. With antihypertensives and ASA as effective primary prevention methods this would raise the overall treatment efficacy for those patients in the intermediate and high-risk CHD categories.^{24, 25}

Finally, the strategy to utilize CAC score to direct therapy differed between studies. Van Kempen et al. used the CAC scores to reclassify patients into a different risk category thus directing pharmacotherapy initiation, while Pletcher et al. used the absolute CAC score to direct statin therapy. This is an important distinction because it assumes a difference in the clinical utilization of CAC score as either an independent or adjunct screening tool.

Conclusion

Whether CAC screening can guide statin therapy as a cost-effective strategy for primary cardiovascular prevention is highly dependent on the cost of screening, statin therapy and the patient's risk factors. Comparing the results of the three CEA directly to each other is difficult as they each assume different estimates and strategies for CAC score utilization. Widespread CAC screening is not cost-effective, but may be so for certain intermediate populations such as men

with a strong aversion to taking a statin pill daily. The decision for providers to recommend CAC screening and prescribe a statin for primary prevention should be a conversation between the patient and provider, knowing that CAC screening adds additional upfront costs. Future CEAs should continue to evaluate the utility of CAC scores guiding statin therapy as additional studies validate accuracy of primary CHD risk-estimation and efficacy of primary statin therapy. Furthermore, cost-effectiveness models are effective ways of estimating the costs, harms and benefits of CAC guiding statin therapy, but may not be able to accurately all aspects of patient and physician behavior variables. Just knowing the CAC score can influence patients uptake of healthy lifestyle changes and change physician prescribing patterns.²⁶ Thus, clinical trials measuring the costs, harms, and benefits of the CAC score guiding statin therapy would be the most accurate way of estimating such outcomes.

Figure 1. Selection of Articles of Review Inclusion

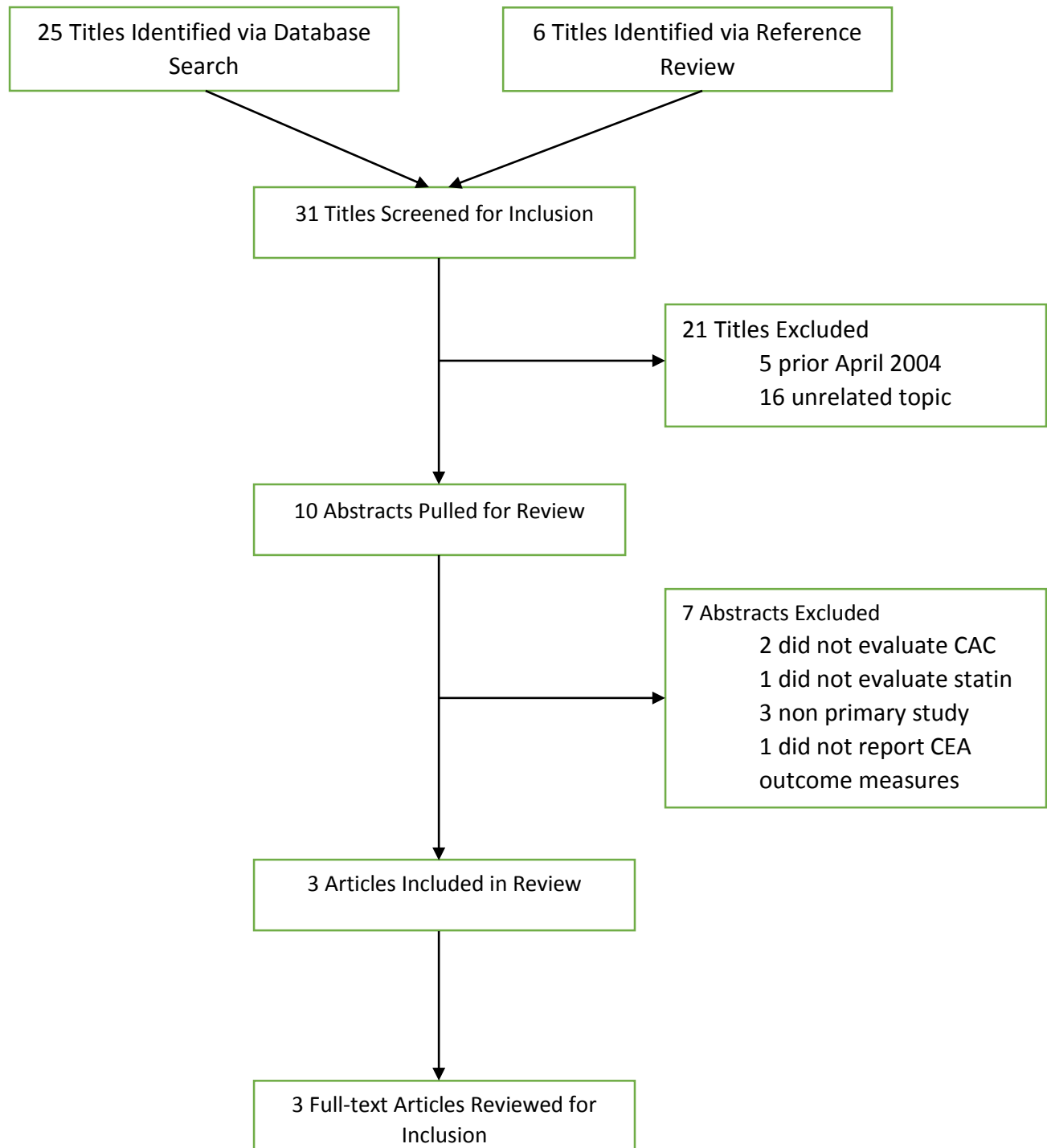


Table 1. Study Characteristics

| Study Citation | Base Case | Main Analytical Method | Screening & Treatments | Optimal Decision | Sensitivity Analysis | Harms Included | Quality Rating |
|------------------------|---|--------------------------------|---|---|-----------------------------|-----------------------|-----------------------|
| Diamond & Kaul 2007 | Asymptomatic middle-aged men & women | Cost-effective analysis (LYEs) | SHAPE vs NCEP vs treat-all statin | Treat-all statin | Partial | No | Poor |
| van Kempen et al. 2011 | Asymptomatic elderly patient with 10-20% 10-year CHD risk | Cost-utility analysis (QALYs) | current practice vs current guidelines vs CAC screening vs treat-all statin | Men: CAC screening Women: Current guidelines | Complete | Yes | Good |
| Pletcher et al. 2014 | Asymptomatic 55 year old woman with 7.5% 10-year CHD risk | Cost-utility analysis (QALYs) | Treat-all statin, treat none statin, Treat if CAC score >0, >100 or >300 | Treat-all statin | Complete | Yes | Good |

Table 2. Quality Assessment Ratings Using Recommendations from the Cost-Effectiveness in Health and Medicine Task Force

| | Diamond & Kaul 2007 | Van Kempen et al. 2011 | Pletcher et al. 2014 |
|---|---------------------|------------------------|----------------------|
| Framework | | | |
| Background and objectives | - | ++ | ++ |
| General framing and design of analysis | + | ++ | ++ |
| Target population | + | + | ++ |
| Other program descriptors (eg care setting, model of delivery, timing of intervention) | + | + | + |
| Description of comparators | + | ++ | ++ |
| Boundaries of the analysis | + | ++ | ++ |
| Time horizon | ++ | ++ | ++ |
| Study perspective | + | + | ++ |
| Data and Methods | | | |
| Description of event pathway | + | ++ | ++ |
| Identification of analysis outcomes | - | + | ++ |
| Description of model | n/a | ++ | ++ |
| Model assumptions | n/a | ++ | ++ |
| Diagram of event pathway | n/a | ++ | ++ |
| Software used | n/a | ++ | ++ |
| Description of estimates of effectiveness, resource use, costs, health states, quality of life states and sources | + | ++ | ++ |
| Methods for obtaining estimates | + | ++ | ++ |
| Critique of data quality | - | - | - |
| Year of cost | | ++ | ++ |
| Method used to adjust cost for inflation | - | - | - |
| Type of currency | ++ | ++ | ++ |
| Source and methods for obtaining expert judgment | - | ++ | ++ |
| Discount rate | - | ++ | ++ |
| Results | | | |
| Results of model validation | n/a | ++ | ++ |
| Reference case results (total costs and | + | ++ | ++ |

| | | | |
|---|----|----|----|
| effectiveness, incremental costs and effectiveness, and incremental cost-effectiveness ratios | | | |
| Results of sensitivity analysis | + | ++ | ++ |
| Other estimates of uncertainty | + | ++ | ++ |
| Graphical representation of cost-effectiveness results | - | ++ | ++ |
| Aggregate cost and effectiveness information | - | ++ | ++ |
| Disaggregated results | - | ++ | ++ |
| Secondary using 5% discount | - | - | - |
| Other secondary analysis | - | - | - |
| Discussion | | | |
| Summary of reference case results | ++ | ++ | ++ |
| Summary of sensitivity results with assumptions and uncertainties | + | ++ | ++ |
| Discussion of analysis assumptions with ethical considerations | + | + | + |
| Relevance of study results for policy or clinical decisions | + | ++ | ++ |
| Results of related cost-effectiveness analysis | + | ++ | ++ |
| Distributive implications of an intervention | + | + | + |

Adopted from Siegal et al. 2006 “Recommendations for Reporting Cost-effectiveness Analysis” from the Panel on Cost-Effectiveness in Health and Medicine Task Force²⁶

(-) indicates area not addressed, (+) indicates area minimally addressed, (++) indicates area adequately addressed, (n/a) indicates area not applicable for specific CEA

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Exploring the Association between Masked Hypertension and Coronary Artery Calcium

Abstract

Introduction: Coronary heart disease (CHD) remains the leading cause of death in the United States despite the widespread knowledge of modifiable risk factors. Elevated blood pressure (BP) is a leading contributing risk factor that may be present in a subset of patients with normal office measurements, but have elevated BP throughout the day as measured by an ambulatory blood pressure monitor (ABPM). This BP phenotype called masked hypertension (MH) carries similar CHD risk as sustained hypertension. Additionally, the presence of coronary artery calcium (CAC) is another independent CHD risk factor that is unknowingly present in many patients. To our knowledge, the association between these two risk factors has not been evaluated. In this study, we examined whether adults with MH were more likely to have CAC as compared to those with sustained normotension.

Methods: This analysis uses data from a larger study that recruited 420 adults aged ≥ 30 years who did not take a BP-lowering medication or did not have a hypertension diagnosis. The participants had measurements of BP in a research clinic and by 24-hour ABPM and were then invited to have a CAC scan. For this analysis, only those participants with nonelevated office BP were included. Based on the pairing of office and ambulatory BP, participants were classified as having MH or sustained normotension. The association with CAC was compared between these groups.

Results: Of the 420 recruited adults, 225 patients received a CAC scan who did not have sustained or white-coat hypertension. The overall prevalence of CAC for those participants was 24%. Among the participants with MH, 26% had CAC while among the participants with sustained normotension, 22% had CAC ($P = 0.53$).

Conclusions: There is a weak association of having CAC with MH when compared to a normotensive BP phenotype that did not achieve statistical significance in our cohort. This association may be difficult to demonstrate because of other factors that increase CAC prevalence. Additional analysis and studies should examine all such variables to more accurately assess the relative importance of MH and other cardiovascular risk factors in contributing to the development of CAC.

Introduction

Atherosclerotic coronary artery disease (CAD) is a major cause of mortality in the United States. Myocardial infarctions (MI) and other forms of coronary heart disease (CHD) cause over 32% of US deaths while costing \$315.4 billion in direct and indirect costs.¹ Many of these events occur in patients without recognized clinical risk factors. One of the most important risk factors is elevated blood pressure (BP). With the advent of ambulatory BP monitoring (ABPM), it has become clear that many people have BP that is considered normal in the office setting but is actually elevated over the course of a typical day. Thus, it is possible that one reason that elevated BP goes unrecognized is that the office BP fails to detect it, a situation called masked hypertension (MH).

ABPM remains the best noninvasive indicator of average BP levels and the optimal way to identify MH.² People with MH have CHD risk levels similar to those with sustained hypertension.³⁻⁶ For example, MH is an independent risk factor for coronary events such as coronary death and stroke.⁴⁻⁷ The prevalence of adult patients with masked hypertension is estimated to be between 10% and 24% with a higher prevalence found in patients with prehypertension or borderline hypertension.^{4-6, 8,9}

The presence of coronary artery calcium (CAC) identified by multi-dimensional computer tomography (MDCT) scan or electron beam computed tomography (EBCT) is an independent predictor of coronary events¹⁰⁻¹² and also provides valuable information to help improve net CHD risk stratification.¹²⁻¹⁴ Sustained hypertension and prehypertension as measured in an office setting have been shown to be associated with CAC prevalence and progression.¹⁵⁻¹⁷ Additionally, hypertension as identified by ambulatory blood pressure monitoring (ABPM) has also been shown to be associated with CAC.¹⁸ To our knowledge, the

association between MH and CAC has not been evaluated. In this study, we examined whether adults with MH were more likely to have CAC as compared to those with sustained normotension.

Methods

Study recruitment and setting

This analysis uses data from a larger study that recruited 420 adults aged ≥ 30 years who did not take a BP-lowering medication and did not have a hypertension diagnosis. The participants were recruited from seven primary care centers via signs announcing a study for people with recent office BP measurements that were “borderline” or a “little high”. Active recruitment was achieved through campus list-serve emails sent every 3-4 months. Study coordinators also recruited potential participants via medical records and vitals documented during their most recent clinic visit. Inclusion criteria required the most recent BP measured in clinic visit to be between 120 and 149 mm Hg systolic or 80 to 95 mm Hg diastolic. Exclusion criteria included pregnancy, dementia, any condition that would preclude wearing an ambulatory BP monitor, persistent atrial fibrillation or arrhythmia. Participants with a BP reading greater than 160/100 mm Hg on the first research office visit were also excluded. Participants were invited to receive an optional CAC scan.

Office BP

Patients underwent check-in procedures at the study visit site and were placed in an exam room. After at least a 5- minute rest, same arm BP was measured 3 times with the subject appropriately positioned¹⁹ using an automatic office-type oscillometric device (Welch Allyn

Vital Signs Welch Allyn, Skaneateles Falls, NY)²⁰ with an appropriately sized cuff. The three measurements were averaged to determine the participant's office BP measurement for the visit.

Ambulatory BP monitoring

At the conclusion of the study visit, participants were fitted with an Oscar 2 oscillometric monitor (Suntech Medical, Morrisville, NC), which has been previously validated.²¹ The monitors were programmed to measure BP at 30 minute intervals from 6am to 10pm and at 1 hour intervals from 10pm to 6am. Participants self-reported a sleep diary to define awake and sleep periods. Those with missing diary information were deemed as having awake time of 10am to 10pm. Maximum BP measurement time was limited to 140 seconds, and the monitors were set for a maximum pressure of 220 mm Hg. Participants were encouraged to wear the cuff for the entire monitoring session and to hold their arm still during reading periods. Faulty readings would trigger a repeat measurement. A minimum of 14 awake sessions and 6 sleep readings were required for an adequate ABPM session. Only awake measurements were included in the analysis as consistent with previous study methods concerning the definition of masked hypertension.

CAC scan

CAC scans were performed on a 64-slice MDCT dual source CT (Somatom Definition, Siemens, Forchheim, Germany). The electrocardiogram signal from the patient was monitored in order to enable synchronization with the scanner. The scan parameters included tube voltage 120 kV, tube current 100 mAs/rotation collimation of 64×0.6 mm and rotation time 330 ms resulting in a temporal resolution of 0.87 ms. Sequential scanning mode was used when heart rate and scan time allowed to minimize radiation exposure, otherwise spiral acquisitions were performed. Approximate radiation exposure was 1-2 mSv for sequential scans and 2-3 mSv for

spiral acquisitions. A standard calcium scoring kernel (B35f) was used for reconstruction of the CT-data. Images were reconstructed with a slice thickness of 3.0 mm. Calcifications were quantified with scoring software (Syngo CaScore, Siemens Medical Solutions). All lesions with a detection threshold of > 130 HU were marked by an experienced observer, and the coronary artery calcium load in each patient was computed using Agatston Scoring.²² All studies were read by a single cardiologist with training and expertise in cardiac CT, blinded to whether the participants had MH or not.

Additional variables

We collected demographic information including age, self-reported race, education and insurance status. Height and weight were measure on the first visit to calculate body mass index (BMI) and arm circumference was measured at mid-bicep to guide selection of the appropriate cuff size.

Analysis

Only participants who completed the CAC scan, office BP and ambulatory BP and who did not have sustained hypertension or white-coat hypertension were included in this analysis. We used the average office BP and awake ABPM to determine the prevalence of masked hypertension. We defined MH as a preceding office BP average $< 140/90$ mm Hg with either a mean awake ABPM systolic BP ≥ 135 mm Hg or mean awake diastolic BP ≥ 85 mm Hg. We compared the percentage of CAC between the two groups and also report the unadjusted odds ratio (OR) for the association between CAC presence and MH with a 95% confidence interval. Additional analyses were calculated to examine whether MH was associated with Agatston score or with a threshold of 100 or 300. We also examined the bivariate association of CAC with age, sex, race and smoking status as these have previously been identified as independent predictors

of CAC.^{17, 23-28} We report the OR of the CAC association with MH adjusted for these covariates as well.

Study Approval

This study was approved by the Office of Human Research Ethics at the University of North Carolina at Chapel Hill.

Results

Participant characteristics

The mean \pm SD age of the study sample was 47 ± 12 years. Most participants were aged 30-49 years (56%) (Table 1). Approximately 75% were white and 21% were black. Most participants were overweight (34%) or obese (38%). Only 7% were current smokers.

From the 420 eligible participants, 108 with sustained hypertension and 5 with white coat hypertension were excluded from this analysis. Of those remaining, 70 participants did not agree to or complete an adequate CAC scan, leaving 225 subjects. Those included in this analysis had very similar distributions of age, sex, race and current smokers compared to the study participants as a whole (Table 1). There were slightly more obese patients in this analysis group (42%) compared to the entire study sample (38%).

Among the included study participants, the proportion who had CAC was 24%. The overall prevalence of MH was 59%. The mean \pm SD office BP at initial research visit was 124/78 \pm 8/7 mm Hg while the mean \pm SD awake ABPM was 139/82 \pm 13/9 mm Hg.

Association between MH and CAC

Among the participants with MH, 26% had CAC while among the participants with sustained normotension, 22% had CAC (P= 0.53) (Table 2).

Older age was associated with the presence of CAC with 43% of participants 50 to 70 years having CAC compared to 10% of participants aged 30 to 49 years ($P < 0.01$). Men also had significantly more CAC present than women, with 39% and 14% respectively ($P < 0.01$). Whites were more likely to have CAC than blacks although the difference was not statistically significant (27% vs 15%, $P = 0.29$). Current smokers were also more likely to have CAC present (31% vs 24%, $P = 0.51$) with a small sample size of smokers ($n = 16$) (Table 3).

When comparing the association between MH and CAC as a continuous Agatston score, those without MH had a mean \pm SD CAC score of 83 ± 633 while those with MH had a mean \pm SD CAC score of 38 ± 246 ($P = 0.45$). There was also a lack of association between CAC and normotensive and masked hypertensive participants when using a threshold of 100 (6% vs 4%, $P = 0.71$) or a threshold of 300 (2% vs 1%, $P = 0.68$) (Table 2).

Participants had slightly greater odds of have CAC present if also having masked hypertension (OR 1.23 [95% CI: 0.63 to 2.44] $P = 0.53$). The association was also adjusted for being above or below 50 years, where the trend remained statistically nonsignificant (OR 1.37 [95% CI: 0.70 to 2.67] $P = 0.35$). Adjusting for sex also saw a nonsignificant trend between MH and CAC present (OR 1.06 [95% CI: 0.55 to 2.04] $P = 0.87$).

Discussion

CAC levels and MH are both independent risk factors for CHD and the potential association had not been explored in previous literature.^{3-6, 10-12} Our analysis found that people with MH tended to have a higher prevalence of CAC than those who were normotensive, although this association was not statistically significant. Masked hypertension is associated with levels of target organ damage that approach those observed in individuals with sustained

hypertension, including increased LV mass index and relative wall thickness, elevated creatinine, and presence of atherosclerotic plaque.²⁹⁻³¹ Additionally, elevated BP is a major determinant of CAC prevalence in adults.^{17, 23-28} Thus, we expected to find an increased prevalence of CAC in our patients with masked hypertension.

Our results could have been influenced by a number of factors that contribute to increased prevalence of CAC in patients without sustained hypertension or masked hypertension. The patients enrolled in our study were recruited with “borderline” or “a little high” BPs. Elevated BP or prehypertension leads to increased amounts of CAC.^{15,16} The participants with sustained normotension had a mean \pm SD office BP of 122/75 \pm 9/7 mm Hg, while participants with masked hypertension had a mean \pm SD office BP of 125/79 \pm 7/6 mm Hg. Although the difference was statistically significant ($P = <0.001$), clinically the 3 mm Hg difference between groups may not have the distinguishing power needed to show a true association. Additionally, when examining CAC levels as a continuous variable, or with a 100 or 300 score threshold, we also found a weak association.

We found a greater associations of MH and CAC with increased age. The literature has shown that age is a determinant of CAC levels.^{17, 23-28} Specifically, Hoff et al. showed in a large cohort of 35,246 asymptomatic adults that CAC presence below the age of 50 was uncommon.²⁶ MH prevalence also increases with age^{32,33} and although we found age was associated with MH and CAC, it was not statistically significant ($P = 0.35$).

We also found increase prevalence of CAC in men versus women which has been addressed in the literature.^{17, 23-28} Increased prevalence of MH has also been found in men versus women³¹⁻³³ which we also found, but the association for MH and CAC was not statistically significant ($P = 0.87$).

Smoking status has been independently linked to both MH prevalence and CAC prevalence. A large 6,083 study of primary care patients in Australia found that smoking independently predicted MH.³² Additionally, Mann et al. found that office BP did not differ between smokers and non-smokers, but that smokers had a higher daytime ABP average of 145 mm Hg compared to 140 mm Hg.³⁴ Smokers also have higher CAC prevalence as described by Shaw et al. who found that nearly half of current smokers in an asymptomatic sample of 10,377 patients had CAC present, while two-thirds of non-smokers did not ($P < 0.0001$).³⁵ Our study found no increased association between MH and CAC, most likely due to the small number of smokers in our analysis (7%).

Other factors associated with greater prevalence of CAC in our non-masked hypertension group may have influenced our results as well. CAC prevalence has been linked to increased body mass, low high density lipoprotein, increased low-density lipoproteins and insulin resistance.³⁶⁻³⁸ One limitation to this study was that our analysis did not examine the possible confounding effects of such variables.

Our definition of masked hypertension only included daytime measurements. This was done in agreement with other masked hypertension study methods as daytime measurements are recommended in order to provide patients with the opportunity to use self-administrated home measurements as well.^{3-6, 39} However, other studies such as Hermida et al. have suggested that using nighttime measurements adds to the prognostic value of CVD risk. They found that the hazard ratio (HR) of those previously defined as “masked hypertension” but with normal asleep BP was comparable to the reference group of normotensives.³⁹ Additionally, Viera et al. found that patients with moderate nighttime BP dipping of around 10% had the lowest levels of CAC.⁴⁰

Future sensitivity analysis using an alternative mean 24-hour BP to define masked hypertension could be done when evaluating the association to CAC.

Conclusion

Masked hypertension is associated with greater CAC prevalence though not statistically significant. Both masked hypertension and CAC are independent risk factors for CHD that are not regularly screened for in clinical practice. Each requires additional resources and evaluation outside of the clinic which makes choosing whom to screen a difficult one for clinicians. A prospective cohort study would be best to assess how masked hypertension is related to CAC in terms of prevalence, progression, CHD events and outcomes.

Table 1. Characteristics of participants

| | Study population (n=420) | | Analysis participants (n=225) | |
|--|-----------------------------|------------|----------------------------------|------------|
| | n | percentage | n | percentage |
| Age | | | | |
| 30-49 | 238 | 57 | 128 | 57 |
| 50-70 | 181 | 43 | 97 | 43 |
| Sex | | | | |
| Male | 183 | 44 | 95 | 43 |
| Female | 237 | 56 | 130 | 57 |
| Race | | | | |
| White | 314 | 75 | 169 | 75 |
| Black | 90 | 21 | 48 | 22 |
| Asian | 11 | 3 | 5 | 2 |
| Other | 5 | 1 | 3 | 1 |
| BMI | | | | |
| Underweight (<18.5 kg/m ²) | 2 | 1 | 1 | 1 |
| Normal (18.5 - <25 kg/m ²) | 114 | 27 | 62 | 27 |
| Overweight (25 - <30 kg/m ²) | 145 | 34 | 67 | 30 |
| Obese (≥ 30 kg/m ²) | 159 | 38 | 95 | 42 |
| Current Smoker | 30 | 7 | 16 | 7 |

Analysis participants included all those eligible for participation, did not have sustained hypertension and were able to complete the CAC scan.

Table 2. Coronary artery calcium levels by BP category (N=225)

| Calcium Score | Sustained normotension (percentage) | Masked Hypertension (percentage) | P-value |
|---------------|--|-------------------------------------|---------|
| = 0 | 78% | 74% | 0.53 |
| > 0 | 22% | 26% | |
| < 100 | 94% | 96% | 0.71 |
| ≥ 100 | 6% | 4% | |
| < 300 | 98% | 99% | 0.68 |
| ≥ 300 | 2% | 1% | |

Table 3. Presence of CAC by covariates

| | Percentage with CAC | P value (if <0.10) |
|-------------------|---------------------|--------------------|
| Age | | |
| Ages 30-49 | 10% | |
| Ages 50 and older | 43% | <0.01 |
| Sex | | |
| Male | 39% | |
| Female | 14% | <0.01 |
| Race | | |
| White | 27% | |
| Black | 15% | |
| Smoking Status | | |
| Smoker | 31% | |
| Nonsmoker | 24% | |

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